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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,317	07/22/2003	Nikolay Korokhov	D6471	1681

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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,317	KOROKHOV ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	waf

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4,11,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of the papers filed on 8/1/2005 is acknowledged. Claims 1-20 are pending. Claims 4, 11 and 19-20 are withdrawn from consideration.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 8/1/2005 is acknowledged. The traversal is on the ground(s) that the Group I and Group II claims are inextricably linked and therefore it would not place an unnecessary burden on the examiner to search and examine the groups together. Furthermore, Applicant argues that a search of Groups I-II would not place an unnecessary burden on the examiner as a search for the Group III methods would necessarily include the Group I and Group II inventions. This is not found persuasive because a search for the inventions of Groups I-III would not be coextensive and thus presents a search burden. The products of Groups I-II require a separate and distinct search because the immunoglobulin-binding domain is inserted at different locations within the adenovirus. Therefore each product has a different mode of operation and a different structure. As such it would be burdensome to search the inventions of Groups I-II together.

The method of Group III requires a separate search because the method comprises steps not present in the claims of Groups I-II and the product of Groups I-II could be used in other methods (e.g. use in a DNA recombination reaction). As such it would be burdensome to search the inventions of Groups I-III together.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-10 and 12-18 are rejected under USC 112, first paragraph, because the specification, while being enabling for an a recombinant adenovirus (Ad) with (i) a heterologous gene, (ii) a wild type Ad5 fiber protein with the immunoglobulin-binding domain (Cd) of Staphalococcus A, and (iii) a gene encoding a fusion protein comprising an immunoglobulin Fc domain and a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody, does not reasonably provide

enablement for *in vivo* targeting of the vector to a cell that expresses a cell surface molecule. Nor does the specification reasonably provide enablement for the *any* adenovirus vector, nor for *any* modified fiber protein utilized in conjunction with *any* immunoglobulin binding domain and/or *any* targeting ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to any targeted recombinant adenovirus vector wherein a fiber protein comprising an immunoglobulin-binding domain binds to an immunoglobulin (Ig) Fc domain fused to a targeting ligand which in turn binds to a cell surface molecule. The claims encompass any adenovirus with (i) a gene encoding a heterologous protein, (ii) a modified fiber protein (any modification from any

adenovirus) comprising an immunoglobulin-binding domain (including antibodies and other large proteins that contain Ig domains), and (iii) a gene encoding a fusion protein comprising a targeting ligand (of any size and conformation) and an immunoglobulin Fc domain.

The nature of the subject is complex because the fiber protein modification must be made in such a way as to allow for functional display of the immunoglobulin-binding domain on the surface of the virus. The Fc domain-ligand fusion protein must also be expressed at amounts abundant enough to allow for a complex to form between it and the virus and the cell surface molecule. Even should the appropriate amount of expression of the soluble Fc domain-ligand fusion molecule be reached, it would have to be secreted with the proper timing and abundance so as to allow for an Ad-Fc binding-domain::Fc-ligand::surface molecule complex to form. Without enough of the Fc-ligand fusion molecule present, the native tropism of the adenovirus would not be inhibited. This is especially problematic in vivo where presence of the natural viral fiber knob would drive Ad(5) vectors to the liver and other cells/tissues that express the Coxsackievirus and Adenovirus receptor (CAR).

Breadth of the claims: The claims are very broad in that they encompass *any* recombinant adenovirus with (i) with *any* gene

encoding a heterologous protein, *any* modified fiber protein comprising an any immunoglobulin-binding domain or *any protein* containing an immunoglobulin-binding domain, and/or (iii) *any* fusion protein comprising a targeting ligand for *any* cell surface molecule. The complex nature of the subject matter is exacerbated by the breadth of the claims.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for *in vivo* adenovirus targeting. Even a review of the state of the art post-filing (Mizuguchi et al, Human Gene Therapy 15:1034-1044, November 2004) concedes that "when systemically administered, vector dissemination, resulting in accumulation in liver, is unavoidable" (page 1037, second paragraph). Mizuguchi also notes that to create a strictly targeted Ad vector, two basic requirements must be met: construction of vectors that abolish natural viral tropism and identification and incorporation of a foreign ligand with high affinity for a specific cellular receptor *into the capsid of the Ad vector*. Furthermore, in an article published post-filing by a group that includes the instant inventors (Korokhov et al. Journal of Virology, 77(24):12931-12940, 2003), Korokhov et al teach that adapter-mediated targeting requires the production and purification of

at least two different components (the virus and the targeting ligand), their subsequent conjugation in a targeting complex, and the purification of that complex from non-reacted components (page 12935). Thus, the claimed recombinant Ad would have to be purified, complexed with the Fc-targeting ligand fusion protein and then purified again before *in vivo* targeting could be achieved.

With regard to a modified fiber protein containing an immunoglobulin binding domain, Everts et al teach that modified Ad fiber proteins must include some essential elements such as a fiber tail for incorporation into the capsid and a trimerization motif to maintain the prerequisite trimeric structure for successful virion assembly (Everts et al. Current Gene Therapy 4: 337-346, 2004; see entire document, especially page 342, third paragraph). Everts et al also describe modified fiber proteins with knob deletions and chimeric fiber proteins and note that not all targeting ligands are compatible with fiber trimerization (page 342). In particular, Everts et al note that the intracellular reducing environment is not compatible with disulfide bond formation and hence correct protein folding. Everts et al also teach that there is a size limitation of peptides that can be inserted into the C-terminus of the Ad

fiber protein before trimerization is inhibited, wherein, in one case, 27 amino acids was found to be above the limit.

Finally, as of the effective filing date, there is no art of record for the successful genetic re-targeting of an Ad vector comprising a genetically modified fiber protein used in conjunction with an adapter molecule produced by the same Ad vector, either *in vivo* or *in vitro*.

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of Ad targeting is highly complex and unpredictable. Indeed, it requires ablation of the natural viral tropism of the Ad vector as well as incorporation of a foreign ligand with high affinity for a specific cellular receptor *into the capsid of the Ad vector*.

Guidance of the specification and existence of working examples: The specification teaches that targeting ligands incorporating a human Fc domain and either an anti-CD40 single chain antibody or CD40L form stable complexes with Ad vectors with fiber proteins comprising an insert of the immunoglobulin-binding domain (C domain, Cd) of *Staphylococcus aureus* Protein A. The 59 amino acid-long Cd was inserted into both the HI loop and at the C terminus of the AD5 wild type fiber protein via a linker sequence. Although the specification notes that this insertion did not affect the yield or growth dynamics that might

be expected by incorporation of such a large domain into this site, it does not teach what structural or chemical properties allow for the insertion of large immunoglobulin-binding domains other than that of the C domain of Protein A. (To that end, Applicant has described a method for screening fiber-C domain species that can be employed for use in their targeted Ad vector.)

Neither does the specification teach how to make and use any modified fiber protein with an immunoglobulin-binding domain. The only other modified fiber protein taught by the specification is a fiber-fibritin chimera (page 28), but the specification provides little or no guidance with regard to other fiber modifications that are encompassed by the claims and little to no guidance on where immunoglobulin-binding domain insertions within such modified fibers would be tolerated or should be made.

The specification also provides little or no guidance on the kinds of Ad vectors which can be targeted in this manner. Applicant states that the high degree of structural similarity of the Ad fiber knob domains from different serotypes predicts the compatibility of the Protein A C domain with the frameworks of fiber knobs other that that of Ad5 (page 18), but the specification provides little or no guidance on where the gene

encoding the Fc-targeting ligand should be inserted in other Ad serotypes or how such serotypes might be used to successfully target the cells of interest and how to do so without unwanted side effects, such as vector-associated immunogenic effects.

The specification includes five examples of Ad vectors with fiber proteins containing the C domain of *S. aureus* and one example of an Ad vector with and Fc-targeting ligand molecule but the specification does not have one example of the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene).

Perhaps most importantly, the specification does not make up for the deficiencies in the art that allow for successful targeting of any of the claimed vectors *in vivo*. Neither of the two basic requirements for targeting of an adenovirus described above have been met, i.e. the specification does not teach a single adenovirus vector wherein the native tropism has been ablated and wherein the targeting ligand with specific high affinity for the cellular receptor has been incorporated into the capsid of the virus.

Amount of experimentation necessary: The quantity of experimentation necessary to make the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the targeted

adenovirus vector commensurate in scope with the claims. In order to determine how to successfully target an adenovirus vector comprising the claimed elements, one of skill in the art would first have to make the adenovirus in such a way as to meet or overcome the requirements for targeting, i.e. ablate the native tropism of the virus and incorporate the targeting ligand with high affinity for the cell surface molecule into the viral capsid. Otherwise, one would have to determine how to produce and secrete sufficient amounts of the Fc-targeting ligand molecule in such a manner as to complex with all exposed, modified fiber proteins to prevent CAR-association and re-target the Ad vector to the proper cell(s). Furthermore, the skilled artisan would have to determine which other immunoglobulin-binding domains are compatible with which Ad fiber proteins, modified or otherwise. The skilled artisan would also have to determine where such immunoglobulin-binding domain insertions could be tolerated without disrupting modified fiber protein trimerization. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the lack of guidance provided by the specification as well as the nature of the invention and the

unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-3, 5-10 and 12-18 are not considered enabled by the instant specification.

Claims 1-3, 5-10 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn toward a targeted recombinant adenovirus vector, comprising (i) a gene encoding a heterologous protein, (ii) a modified fiber protein comprising an immunoglobulin-binding domain, and (iii) a gene encoding a fusion protein comprising a targeting ligand and an immunoglobulin Fc domain, wherein binding of said immunoglobulin-binding domain to said Fc domain connects the targeting ligand to said modified fiber protein, thereby targeting said adenovirus vector to a cell that expresses a cell surface molecule that binds to said targeting ligand. The claims encompass *any* recombinant adenovirus vector, *any* modified

fiber protein with *any* immunoglobulin-binding domain, and/or a gene encoding *any* fusion protein comprising a targeting ligand and an immunoglobulin Fc domain wherein binding of the Ig-binding domain to the Fc domain connects the targeting ligand to the modified fiber protein, thereby targeting the vector to a cell that expresses a cell surface molecule that binds to the targeting ligand.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation and any combination thereof. The specification describes five examples of Ad vectors with fiber proteins containing the C domain of *S. aureus* and one example of an Ad vector with and Fc-targeting ligand fusion molecule, but the specification does not describe one example of the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene).

Even if one accepts that the specification teaches in general terms *how to make* a very small subgroup of vectors with one or two examples of a modified fiber protein, an

immunoglobulin-binding domain, a gene encoding a Fc-ligand fusion protein, and a heterologous gene, the specification does not describe how any of those vectors, once made, would of themselves thereby target the Ad vector via the claimed binding interactions (see *State of the art* and *Guidance and examples provided by the specification* above).

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the lack of description provided by the prior art and specification with regard to the sequences capable of targeting a recombinant adenoviral vector, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of Ad vectors capable of targeting to a cell surface molecule. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those Ad vectors that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1-3, 5-10 and 12-18.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant does submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

October 14, 2005

TERRY MCKELVEY
PRIMARY EXAMINER